DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

CBER REGULATORY REVIEW MEMORANDUM

Date 08 December, 2014

From Dr. Claire H. Wernly,
Laboratory of Microbiology, In-Vivo Testing and Standards (LMIVTS)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To Biologics License Application Submission Tracking Number # 125562/0

Subject BLA: Review of Sterility, Bioburden and Bacterial Endotoxin Test Qualifications for Anthrasil™, Anthrax Immune Globulin Intravenous (Human) [AIGIV].

Through Dr. James L. Kenney, Chief, LMIVTS/DBSQC/OCBQ/CBER/FDA
Dr. William M. McCormick, Director, DBSQC/OCBQ/CBER/FDA

Applicant Cangene Corporation (operating as Emergent BioSolutions)

Product Anthrasil™, Anthrax Immune Globulin Intravenous (Human) [AIGIV].

Biologics License Application (BLA) Submission Tracking Number (STN) 125562/0

Submission Received by CBER 28 July, 2014

Review Completed 08 December, 2014

Material Reviewed

Method qualifications for: 1) bioburden (b) (4) sterility performed on the drug product (DP); and 3) (b) (4) endotoxin test (b) (4) performed on the DP.

Executive Summary

After a thorough review of this BLA, and the response to CBER's Information Requests (IR) (Amendments 125562/0.3 and 125562/0.11 - received on 25 September, 2014 and November 14, 2014 respectively), this reviewer finds Cangene Corporation's bioburden, sterility, and (b) (4) methods were qualified in accordance with (b) (4) respectively, by demonstrating the Anthrax Immune Globulin Intravenous (AIGIV) matrix is suitable for these intended test methods.

Background

On July 25, 2014, Cangene Corporation (doing business as Emergent BioSolutions) submitted a BLA for Anthrax Immune Globulin Intravenous (Human) [AIGIV] (proposed proprietary name: Anthrasil™). AIGIV is a sterile gamma globulin (IgG) fraction of human plasma containing antibodies to *Bacillus anthrasis.* AIGIV is prepared from Source Plasma obtained from healthy donors immunized with BioThrax® (Anthrax Vaccine Adsorbed) and is indicated as treatment for adult and pediatric patients with toxemia associated with inhalational anthrax. The resultant polyclonal IgG is a passive immunizing agent that neutralizes anthrax toxin by binding to the anthrax protective antigen (PA) and other potential antigens present in BioThrax®.

The final product is a clear to slightly opalescent colorless liquid presented in a 50ml vial. Each vial contains ≥ 60 Units/vial (based on a target potency of (b) (4)) of activity as determined by the Toxin Neutralization Assay (TNA) and is formulated in 10 g% maltose (10 grams of solute [maltose] {excipient/stabilizer} per 100 grams of solution) (excipient/stabilizer) and 0.03% (w/w) polysorbate 80 (excipient/surfactant) without preservatives. AIGIV is intended for single use by intravenous (IV) administration and has been shown to be beneficial in combination with appropriate antibacterial drugs.

The Division of Biological Standards and Quality Control (DBSQC) reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications. Therefore, this review will focus on: 1) bioburden method (b) (4) sterility method performed on the DP; and 3) (b) (4) method performed on the DP.

Review

Bioburden Test Qualification (b) (4)
(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

CBER IR Question

In order to comply with (b) (4) CBER finds the (b) (4) Report (STM 500114) (QCM_MS_0021_rep_v1) for bioburden test of (b) (4) incomplete since it does not include an evaluation of (b) (4) lease provide comparable data (to include lot numbers and relevant negative controls) for indicator microorganisms and sample controls to include the use of (b) (4).

Cangene's Response

Cangene Corporation (Cangene) acknowledges that only the (b) (4) *was assessed for the method suitability studies. Since the in-process bioburden test is routinely performed on* (b) (4) *, method suitability was performed using only the* (b) (4)

The in-process bioburden method was initiated in response to a 2010 FDA audit to replace the (b) (4) *test and has been accepted in support of other currently FDA licensed hyperimmune products manufactured by Cangene. The* (b) (4) *is not performed as part of routine product testing; therefore, there are no results or suitability data to show. However, there is a* (b) (4) *(QCM_MS_0021).*

CBER finds the response acceptable based on review of the submitted Suitability Test Report (STM 500114) (QCM_MS_0021_rep_v1) and Cangene's response to the IR which states that: 1) the bioburden test method is an in-process test method, not a release method and 2) Cangene performs a (b) (4)

Sterility Test Qualification for AIGIV Drug Product

Cangene Corporation qualified their AIGIV DP using the (b) (4) by performing (b) (4) qualification studies on three lots (b) (4) finished drug product (i.e., numbers:) to demonstrate their matrices are suitable for the intended test method. Cangene Corporation qualified their AIGIV DP matrix (b) (4)

(b) (4)

The test was performed and compliant with (b) (4) and the test results indicate there is no product inhibition on microorganism growth; thus indicating AIGIV matrix for the DP is suitable for testing via the (b) (4) sterility test method.

(b) (4) Endotoxin Test (b) (4) Method Qualification

Cangene Corporation qualified their (b) (4) test method using three lots ((b) (4) of their AIGIV finished drug product to verify their product matrix is suitable for the intended test method.

Samples were tested at the following dilutions (b) (4) (b) (4)

All test parameters for (b) (4) endotoxin qualification were within those approved in their validation procedure and were compliant with the requirements in (b) (4)

- Correlation coefficient (r) of the standard curve (b) (4) ;
- Endotoxin activity of the negative control below quantification limit (λ), (b) (4) ;
- Recovery rate of the spiked endotoxin in the product dilution (b) (4) ; and
- Sample % CV: (b) (4)

The (b) (4) endotoxin concentration results found during the inhibition / enhancement testing were (b) (and were within their release specification of (b) (4) .

Conclusions

After a thorough review of the information submitted in this BLA, this reviewer finds Cangene Corporation's bioburden, sterility, and (b) (4) methods were qualified in accordance with (b) (4) , respectively, by demonstrating that the matrix for both the AIGIV (b) (4) DP is suitable for these intended test methods.